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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,356	07/24/2003	Michael R. Hale	VPI/00-122 DIV2 US	1551
27916 7590 08/27/2007 VERTEX PHARMACEUTICALS INC. 130 WAVERLY STREET CAMBRIDGE, MA 02139-4242			EXAMINER ANDERSON, REBECCA L	
			ART UNIT 1626	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/626,356	Applicant(s) HALE ET AL.	
	Examiner Rebecca L. Anderson	Art Unit 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 June 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13, 18-23 and 27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-13 and 18-23 is/are allowed.
- 6) ☒ Claim(s) 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-13, 18-23 and 27 are currently pending in the instant application.

Claims 1-13 and 18-23 appear allowable and claim 27 is rejected.

Response to Amendment and Arguments

Applicant's amendment and arguments filed 18 June 2007 have been fully considered and entered into the application. Applicants' amendment has overcome all but the 35 USC 112 1st paragraph rejection of claim 27. In regards to claim 27, 28, 30, applicants' arguments have been considered but they are not persuasive.

Applicant argues that a link has been established between ERK kinase activity and the various cancers claimed in the evidence provided on January 25, 2007, referencing the arguments in regards to Kortylewski, Hoshino, and Putz. Applicant argues that these references clearly show that there is a reasonable correlation between the activation of ERK in various cancers, the use of an ERK inhibitor to inhibit cancer cell growth, and the use of the ERK inhibitors of the invention to treat the cancers recited in claim 27. This is not persuasive as the references provided do not disclose compounds of similar structure and therefore do not provide a correlation of the use of the ERK inhibitors of the invention to treat the cancers recited. The references provided do not disclose compounds of similar structure to the claimed invention. See wherein Kortylewski is concerned with PD098059. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cancers. Hoshino,

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Kortylewski, Putz and Frey provided are drawn to in vitro activity, the uses covered by the claims are not enabled based solely on the assay testing. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Lastly, some of the references provided are speculative, see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. Hoshino is speculative in that specific inhibitors may be developed against signaling molecules such as MPA kinases and MEK for cancer therapy, page 820. Kortylewski is speculative in that there is potential of novel therapeutic approaches targeting members of the Ras-Raf-MAPK pathway in the treatment of human melanoma. Frey is speculative in that the studies suggest that the Ras/MAPK pathway may be one of the important signaling pathways that mediate the growth inhibitory response to TGF β in untransformed epithelial cells, page 42. Therefore, the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cancers.

Applicant argues that a skilled artisan would be able to discern an appropriate dosage and method of use based upon the information provided in the specification along with the general knowledge of one skilled in the art. This argument is not persuasive as the only direction or guidance present in the instant specification is the

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listing of diseases applicant considers as treatable by the inhibition of ERK and AKT found on pages 50-53, 45 and 46. There are no working examples present for the treatment of any type of cancer. Test assays and procedures are provided in the specification at pages 58-63 for only AKT3 and ERK2.. However, the disclosure does not provide how this in vitro data correlates to the treatment of the assorted list of cancers of the instant claims. Further, there is no disclosure regarding how all types of cancers having diverse mechanisms are treated. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult cancers embraced by the instant claims. Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Applicant argues that the examiner has not met the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. This argument is not persuasive as there is reason to doubt the objective truth of the statements contained in the specification relied on for enabling support as the state of the prior art is that the pharmacological art involves screening in vitro and in vivo to

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determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Applicants claims are for the treatment of various cancers. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Applicant argues that Hoffman v. Klaus, 9 USPQ2d, 1657 and Ex parte Powers, 220 USPQ 925 does not offer evidence that is inconsistent with applicants' argument that the in vitro data presented correlates to an in vivo use of the compounds of the invention for the treatment of various cancers. This argument is not persuasive as the uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP 2164.05(a).

Applicant argues that the Examiner has characterized the evidence presented by applicants as "speculative" and that this does not meet the Examiner's burden of showing a lack of correlation between in vitro behavior of the compounds of the invention and the therapeutic method recited by claim 27. This argument is not persuasive as the examiner has provided there is reason to doubt the objective truth of the statements contained in the specification relied on for enabling support as the state of the prior art is that the pharmacological art involves screening in vitro and in vivo to

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determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols. The Examiner has stated that some of the evidence provided is "speculative" to show that the evidence provided has been weighed for and against correlation to the

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condition and support has been found that correlation does not exist in the state of the prior art as the state of the prior art has been provided by the examiner as the varying cancers having different treatment protocol and having unpredictability in the art. The evidence provided by applicant has not overcome the evidence cited by the Examiner as the references provided by applicant do not disclose compounds of similar structure and therefore do not provide a correlation of the use of the ERK inhibitors of the invention to treat the cancers recited, additionally some of the references provided are speculative, see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. Therefore, the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the compounds of the claims and to extrapolate to the in vivo treatment of the claimed cancers.

Applicant argues that In re Ruskin 148 USPQ 221 and Ex parte Powers 220 USPQ 925 do not support that the examiner has the authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. This is not persuasive as applicants' specification does not provide any data for the treatment of any cancer claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claim 27 is the method of treatment of a disease selected from colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, and prostate cancer.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the above listed diseases, whether or not the disease is effected by the inhibition of AKT and ERK would make a difference.

Applicants are claiming methods which include the treatment of various cancers.

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Applicants claims are for the treatment of various cancers. The state of the prior art is that cancer therapy remains highly unpredictable. The various types of cancers have different causative agents, involve different cellular mechanisms, and consequently, differ in treatment protocol. It is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy (Golub et al. page 531) Furthermore, it is known that chemotherapy is most effective against tumors with rapidly dividing cells and that cells of solid tumors divide relatively slowly and chemotherapy is often less effective against them. It is also known in the prior art (Lala et al. page 91) that the role of NO in tumor biology remains incompletely understood with both the promotion and inhibition of NO mentioned for the treatment of tumor progression and only certain human cancers may be treated by selected NO-blocking drugs. These example shows that there are different cellular mechanisms, the unpredictability in the art and the different treatment protocols.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the inhibition of AKT and ERK one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role the inhibition of AKT and ERK and, for example, since it is known that the challenge of cancer treatment has been to target specific therapies to pathogenetically distinct tumor types, that cancer classification has

been based primarily on morphological appearance of the tumor and that tumors with similar histopathological appearance can follow significantly different clinical courses and show different responses to therapy.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of diseases applicant considers as treatable by the inhibition of ERK and AKT found on pages 50-53, 45 and 46. There are no working examples present for the treatment of any type of cancer.

Test assays and procedures are provided in the specification at pages 58-63 for only AKT3 and ERK2. However, the disclosure does not provide how this in vitro data correlates to the treatment of the assorted list of cancers of the instant claims.

The uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of in vivo use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be

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embraced in response to this action. See MPEP 2164.05(a).

Further, there is no disclosure regarding how all types of cancers having diverse mechanisms are treated. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult cancers embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is the treatment of a disease selected from colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, and prostate cancer.

Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what cancers would be benefited (treated) by the inhibition of AKT or ERK and would furthermore then have to determine which of the claimed compounds would provide treatment of which cancer, if any.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment of a disease selected from colon cancer, kidney carcinoma, lung cancer, melanoma, ovarian cancer, pancreatic cancer, and prostate cancer, as a result necessitating one of skill to perform an exhaustive search for which cancers can be treated by what compounds of the instant claims in order to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday from 6:00am until 2:30pm.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*/Rebecca Anderson/
Primary Examiner, AU 1626*

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21 August 2007